THE COUNCIL FOR TOBACCO RESEARCH - U.S.A., INC.

110 EAST 59TH STREET
NEW YORK, N. Y. 10022

Application For Research Grant

OCT 16 1972

Date: 10/4/72

1. Name of Investigator(s): (include Title and Degrees)
Harold J. Sobel, M. D.* Director of Laboratories
Ruth Schwarz, M. D. Attending Pathologist

2. Institution & Address: Beth Israel Hospital, 70 Parker Ave., Passaic, N. J. 07055

* Dr. Sobel is also Clinical Associate Professor of Pathology, Columbia University College of Physicians & Surgeons and Special Research Consultant, Zoology & Physiology, Rutgers University

3. Short Title of Project:

Effect of Smoke Inhalation of Asbestos Sensitized Hamsters

4. Proposed Starting Date:
Any time after January 1, 1973

5. Anticipated Duration of this Specific Study:
One year

6. Brief Descripton of Objectives or Specific Aims:

A. The purpose of this experiment is to determine whether true bronchogenic carcinomas (as evidenced by invasiveness, metastases and ordinary morphologic criteria) resembling those of man can be produced by maximal smoke inhalation in asbestos (chrysotile) sensitized hamsters.

B. In addition we will study the normal and experimentally altered respiratory tract of these animals, using morphologic procedures for the visualization of all cell organelles at the level of the light and electron microscopes; as well as both ultra-structural and histochemical methods for the study of mucopolysaccharides. This work will be undertaken as part of a study presently under way in this laboratory.

C. By subtracting the non-precancerous lesions in the controls from the precancerous ones in the experimental animals (if they develop cancers) and with the special morphologic studies described a better understanding of tumor formation in this system should be forthcoming.

7. Epidemiologic studies indicate that asbestos potentiates the possible carcinogenic effect of tobacco smoke in man (eight times).[2] The carcinogenic effect of benzo(a)-pyrene (BP) in hamster lung is potentiated by asbestos (chrysotile) which by itself will not produce lung tumors in the hamster.[3] An almost 100% incidence of lung tumors can be produced in hamsters with BP and chrys at levels of BP that induce considerably fewer tumors when used alone. Asbestos is an extremely common contaminant of man, and most workers feel that lung cancer is induced by a complex of factors.[4] From this data it seems logical that the maximal exposure of hamsters to tobacco smoke (using low nicotine high tar cigarettes) following treatment with chrys would be a meaningful way to determine the relatjve carcinogenicity of tobacco inhalants.

7. Give a Brief Statement of your Working Hypothesis:

See above

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8. Details of Experimental Design and Procedures: (Attach Separate Pages)

We chose the hamster for this work because of their ability to withstand this type of experiment as well as our ability to produce a high incidence of lung tumors in them with chrys and BP.[3] We anticipate using a strain that behaved well in a similar study the LVG:LAK male (Lakeview Hamster Colony (now Carworth), Newfield, N. J.).[3] We chose not to use mice because of the difficulty in intubating large numbers of these rodents and their ability to filter inhalants well in their upper respiratory passages. The susceptibility of rats to respiratory problems in this type of study and their inability to tolerate asbestos inhalation as well as the slow response of guinea pigs to carcinogens and the anatomic difficulties in intubating them ruled them out for use in this study.

In previous studies asbestos (chrys) controls did not develop lung cancers[3] but a virtual 100% incidence of lung cancers could be produced by the additional instillation BP. The incidence at various dose levells of BP was higher when chrys was present. This data suggests that the exposure of hamsters to tobacco inhalants following sensitization by chrysotile instillation would be a meaningful way to determine the relative carcinogenicity of tobacco inhalants. The basis for the use of asbestos as a cocarcinogen are epidemiologic studies indicating that asbestos potentiates the carcinogenic effect of tobacco smoke in man (eight times).[2] Most workers feel that lung cancer is induced by a complex of factors and it is felt that the common contamination by asbestos fiber inhalation is a significant common

(continued on Page 5)

9. Physical Facilities Available (Where Other than Administering Organization Indicate Geographical Location)

See appended material Page 6.

10. Additional Requirements:

The laboratories are fully equiped and functioning. The only additional requirements are: (1) The CTR smoking apparatus which we understand will be supplied. (2) High tar low nicotine reference cigarettes which we understand will be supplied. (3) Carworth disposable plastic cages which will save personnel time required in maintaining this large number of animals and will in the long run be a saving to the grant. Cost will be $1,000.

11. Biographical sketches of all principal and professional personnel (append)

See appended material Page 7 et seq.

12. List of publications: (Five most recent as pertinent) (append)

See references Page 9 et seq.

13. Budget: (1st year)

A. Salaries (Personnel by names)	% time	Amount
Professional		
Harold J. Sobel, M. D.	50%	None
Ruth Schwarz, M. D.	30%	None
William E. Smith, M.D.	Consultant	
Technical		
Eugene Marquet, M. A.	100%	R
Animal room technician	100%	
Animal room aide	50%	provided by hospital
* Including fringe benefirs	Sub-Total	22,000*
B. Consumable Supplies (list by categories)		
Animals		500
Cage supplies		1,000
Food		1,500
Chemicals, books, journals		500
	Sub-Total	3,500
C. Other Expenses (itemize)		
Illustration and chart preparation		250
Page costs and reprints		750
Travel (experimental pathology and cancer meetings and institutions doing similar work)		500
	Sub-Total	1,500
D. Permanent Equipment (itemize)		
None		
E. Overhead (15% of A + B + C)		4,050
	Total	31,050

Estimated Future Requirements:

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Overhead	Total
Year 2	Not applicable					
Year 3	Not applicable					

It is understood that the applicant and institutional officers in applying for a grant have read and found acceptable the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Signature [redacted]
Director of Project Harold J. Sobel, M. D.
201-473-8100 EX234 Telephone

Signature [redacted]
Business Officer of the Institution
David Wachs, Administrator
201-473-8100 EX221 Telephone

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Other Sources of Financial Support

List financial support for research from all sources, including own institution, for this and/or related research projects.

	Title of Project	Source	Amount	Duration
Current *	None			
Pending	Morphochemistry of Aging Alterations in Drosophila **	N.I.H.	$116,100	** Three years

* The hospital has subsidized my research by providing me with one full time and one half time pathologist (the department could easily be handled by me or either of my associates with no additional help), research laboratory space equal to that of the routine laboratory or about 10 hospital beds of this 200 bed hospital (see 9), a modern animal room, and secretarial and ancillary personnel. The research laboratory is fully equipped for electronmicroscopic and histochemical work (see 9). In addition the hospital has absorbed occasional small deficits in research funds.

** Direct costs only, competing application

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denominator.[4] In fact, in 500 consecutive autopsies of subjects over the age of 15 in both Cape Town, South Africa and Miami, Florida asbestos bodies were found in lung smears of no less than 30 per cent of the males and 20 per cent of the females. The incidence was similar in both cities.[5]

A. Soft chrysotile (approximate length 67 microns) and harsh chrysotile (approximate length 36 microns) will be prepared by the method of Badollet and Gantt[6] and tested for the presence of nickel, chromium and other potential carcinobens by emission spectroscopy.

The asbestos will be instilled intratracheally with glass pipettes under direct visualization while tha animals are under nembutal anesthesia. This procedure has been standardized in our laboratory and was taught us by our consultant, Dr. Smith. Each instillation will be 0.1ml. The animals receiving asbestos will receive twelve weekly injections as follows: 2.5mg harsh chrys X2, then 1.0mg soft chrys X2, then 1.25mg soft chrys X3, then 0.25mg soft chrys X5. There is little difficulty in administering the harsh chrys. The soft chrys must be given in smaller doses to avoid suffocation by the gel formed. We will use a suspension in saline with Tween. The above regime is entirely possible in our hands, and was found to be a potent cocarcinogen in previous work.[3]

Using the CTR smoking machine and low nicotine high tar cigarettes, we will attempt to maximally smoke the animals so treated. We contemplate adjusting the animals to the smoking machine for a short time prior to the asbestos administeration and to continue to smoke them during the interval during which the asbestos is being administered. It may be necessary to somewhat alter the smoking schedule immediately following administration of asbestos.

We plan to use a total of 50 cage controls, 100 sham smoked animals and 100 tobacco smoked animals. Half of each group will be treated with asbestos (Fig. 1). We contemplate including a few extra animals in each of the asbestos treated groups to compensate for the early loss of a small percentage of these animals.

B. As part of an ongoing study in this laboratory tissue from control and experimental animals will be studied. With ordinary histological methods, and with histochemical methods as previously outlined by one of us (H.S.).[1] This system enables us with the light microscope, using relatively large pieces of tissue to distinguish cellular organelles and study their size, number, shape and distribution. The techniques used also provide some biochemical information although quantitative data cannot be obtained with histochemical methods. The information obtained with the light microscope with its wide scope will be searched for with the electron microscope. Some alterations are not found in great frequency, but when noted with the light microscope will be found with the EM if they are searched for diligently. On occasion an EM finding which was thought to correlate with the light cytochemical observation was shown not to do so with EM cytochemical preparations which will also be obtained. This is illustrated in my work with 131_I injury of thyroid ref. 23, 35 and 36.

The characterization of muconolysaccharides by the methods of Spicer including EM methods where applicable should also provide a great deal of insight into the alterations associated with carcinogenesis.

These methods will be used in the differentiation of precancerous from non-precancerous lesions.

C. In future studies asbestos sensitized animals can be used in an attempt to assess the carcinogenicity of other factors.

9. Facilities Available

The work will be carried out in a well equipped department of pathology. The routine laboratory consists of separate units for hematology, bacteriology, chemistry, blood bank, washroom for glassware, office for secretary, office for associate pathologist and storage space for slides, etc. Space occupied by these units totals approximately 100' X 80'. Rooms which are partially used for research and partially for routine work are the office of the principal investigator (18' X 12') and the room for the preparation of routine histological sections (18' X 12'). Space devoted exclusively to research consists of the electron microscopy laboratory, histochemical laboratory and a 20' X 12' air-conditioned and heat controlled animal room which is able to house at least 400 hamsters and other small animals if required. The electron microscopy laboratory consists of the room used for cutting and preparing tissue sections (18' X 20'), the dark room (8' X 8') and the room housing the electron microscope (9' X 11'). Histochemistry occupies a space 18' X 17'. The electron microscope is an RCA model EMU-3F, there are 2 LKB and 1 Porter-BLUM ultratoms and diamond knives for preparation of ultra thin sections, a high vacuum evaporator, the necessary incubators, pH meters and vacuum pumps in addition to the usual routine equipment such as an autotechnicon, microtomes and knife sharpening machine, automatic glassware washer and a Zeiss microscope with complete automatic photographic outfit. The histochemical laboratory houses a cryostat recently purchased by the hospital, Sartorius freezing microtome, and ample refrigeration space. The dark room contains all necessary tools for the processing of electron micrographs.

Two experienced and very capable associate pathologists have been provided by the institution so that the grant effort will not be unnecessarily interrupted by hospital routine. Secretarial and some animal maintainence personnel are also provided by the hospital

11. Dr. Sobel's curriculum vitae is attached. He was born in N.Y.C. on R and is R He was trained as an experimental pathologist at the Mount Sinai Hospital, N.Y.C. (see curriculum vitae) and his major interests are in histochemistry, electron microscopy and autoimmune diseases. He is a frequent reviewer for the Journal of Histo- and Cytochemistry. Dr. Sobel's bibliography is attached.

Dr. Schwarz is a capable, board certified, pathologist who handles the routine pathology at this institution and has sufficient time available to spend 10+ hours in research as well. She was born R She was trained under Dr. Max Wachstein which is sufficient to explain her abilities in research, and is a graduate of University Lausanne, Medical School. She is co-author with me of my references 43, 45, 47, 48, 57-59, 61-63 and 65 as well as: (1) Wachstein, M. and Schwarz, R.: Occurrance of Hemorrhiagic Centrolobular Necrosis in Protein Deficient Rats. Proc. Soc. Exper. Biol. Med. 103, 478, 1960. (2) Wachstein, M., Schwarz, R., and Besen, M.: Electron Microscopy and Enzyme Histochemistry of Tubular Regeneration in Rat Kidney (abstract) Federation Proceedings 23, 546, 1964.

Mr. Marquet is a fine research technician and electronmicroscopist who was born R He received a B.S. from Queens College (1962) and a M.S. from St. John's University (1965) and has had considerable experience in electronmicroscopy in my laboratory and in that of Dr. R. Terry at the Albert Einstein College of Medicine since 1965. He is co-author with me of my references 45-50, 54, 58, 59, 61-63, 65, 67 and 69. He is extremely capable in the design, maintainence and repair of mechanical equipment. He is exceptional in the care of the electron microscope and does remarkable work with radios and automobiles. He built his own home. A very exceptional home. He would be a boon to the CTR and invaluable to the experiment in the use and care of the smoking machine.

Dr. William E. Smith is Director of the Health Research Institute at Fairleigh Dickinson University, Madison, New Jersey. He has extensive experience in experimental carcinogenesis, especially in cancer caused by chemicals and dusts in hamsters, mice and rats and has published some 35 papers in this field. He received his A.B. 1934, Princeton, N.J. and M.D. 1938, John's Hopkins School of Medicine. Dr. Smith was a Fellow in Bacteriology in Harvard Medical School 1938-39, Fellow in Medicine Massachusetts General Hospital 1940-41, Assistant in Bacteriology, Harvard Medical School 1941-43, Assistant in Pathology, Rockefeller Institute 1943-47, Associate Sloan Kettering Institute 1947-49, Assitant Professor 1952-56. His pioneering work and experience with asbestos and lung cancer are a boon to this study.

CURRICULUM VITAE

Harold John Sobel, B.A., M.D.

Brooklyn College, Brooklyn, N. Y.
Feb. 1947 to June 11, 1950 - B.A. Cum Laude

The Chicago Medical School, Chicago, Illinois
Sept. 1950 to June 26, 1954 - M.D.

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Harold John Sobel, B.A., M.D.

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FIGURE I.

Number of Hamsters in each Experimental Group

	No Asbestos	Asbestos*
Cage Control	25	25
Sham Smoked	50	50
Tobacco Smoked*	50	50

* for dosage regimen see 8 (details of experimental design) pages 2 & 5 -